Abstract 250 Words
Text 3475 Words
References 41
Figures 1
Tables 4
Supplementary Tables 2

AMBULATORY BLOOD PRESSURE VARIABILITY INCREASES OVER A TEN-YEAR FOLLOW-UP IN COMMUNITY DWELLING OLDER PEOPLE.

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Short Title: ABPV Increases Over Ten Years in Older People

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ABSTRACT

Background: greater ambulatory blood pressure variability (ABPV) is associated with end-organ damage and increased mortality. Age related changes in the cardiovascular and autonomic nervous systems make age associated increases ABPV likely. Cross-sectional studies support this hypothesis, showing greater ABPV among older compared to younger adults. The only longitudinal study to examine changes in ABPV, however, found ABPV decreased over 5 years follow-up. This unexpected observation probably reflected the highly selected nature of the study participants.

In this longitudinal study, we assessed changes in ABPV over ten years in a community-cohort of older people. In addition, we examined the extent to which ABPV was predicted by demographics, cardiovascular risk factors and medication.

Methods: clinical examination & 24 hour ambulatory blood pressure monitoring were carried out at baseline and at 10 years follow-up in 83 people, median age 70 years. ABPV was calculated using standard deviation (SD) and co-efficient of variation (Cv). Three time periods were examined; daytime, nighttime and 24 hours.

Results: daytime and 24 hour, systolic and diastolic, SD and Cv were significantly greater at follow-up than at baseline ($P<0.001$ in all cases). Mean BP did not change.

Multilevel modelling showed follow-up interval had a significant, positive effect on SD and Cv ($P<0.004$), independent of age, sex and medication.

Conclusions: ABPV increased over a ten-year follow-up despite stable mean BP. ABPV may therefore be an additional target for treatment in older people. Future studies should examine what degree of ABPV is harmful and if control of ABPV reduces adverse outcome.

ABREVIATIONS

ABPM	Ambulatory blood pressure monitor
ABPV	Ambulatory blood pressure variability
ACE	Angiotensin converting enzyme
BMI	Body mass index
BP	Blood pressure
Cv	Co-efficient of variation
IQR	Inter quartile range
NICE	National Institute for Health and Care Excellence
SD	Standard deviation
UK	United Kingdom

INTRODUCTION

Ambulatory blood pressure monitors (ABPM) record mean blood pressure (BP), and blood pressure variability. Current UK guidelines recommend routine use of ABPM in the diagnosis of hypertension [1,2]. Mean ambulatory BP is a well-recognised predictor of cardiovascular and all-cause mortality [3-8]. More recently it has been recognised that ambulatory blood pressure variability (ABPV) also carries important prognostic information independent of mean BP. Increased ABPV is associated with: carotid artery damage, progression of small vessel disease, cognitive decline, left ventricular hypertrophy, increased cardiovascular events and increased all-cause mortality [9-17].

It is now widely excepted that mean systolic blood pressure increases with age. However few studies have examined how ABPV changes as people get older. A small number of cross-sectional studies have found that ABPV is higher in older adults compared to younger adults [10,18,19]. This is in keeping with previous studies that have shown that increased ABPV is associated with decreased baroreceptor sensitivity [20-23] and that baroreceptor sensitivity decreases with age [24 25]. It is, therefore, surprising that the only longitudinal study to examine ABPV found ABPV decreased over a five year follow-up [26].

Great strides have been made in controlling mean blood pressure. Mean blood pressure and BP variability are correlated but it is not clear if control of mean BP inevitably stabilises BP variability. Recent studies have suggested calcium channel blockers and diuretics have greater impact on ABPV compared to other antihypertensive classes and animal studies have shown reduction in ABPV to be associated with decreased end organ damage [27-29].

These data suggest that monitoring and controlling ABPV maybe an additional method of moderating cardiovascular risk. It is therefore important to understand how ABPV changes overtime, its relationship to change in mean blood pressure and if there are antihypertensive class effects on ABPV.

We hypothesise that age related changes in the cardiovascular and autonomic nervous systems, resulting in decreased baroreflex sensitivity and increased neurocardiovascular instability, will result in increased ABPV over time and that Goldstein's unexpected findings reflected an unrepresentative exceptionally healthy older population [26].

This longitudinal study aimed to assess changes in ABPV over a ten-year follow-up and examined if these changes were associated with mean BP or prescribed antihypertensive medication.

METHODS

Between April 2002 and October 2003, 353 community dwelling people aged 65 years and older took part in the first phase of a longitudinal study examining neurocardiovascular function in older people. Participants were recruited from a single general practice in the North of England. Persons living in residential care were excluded. Full details of recruitment have been previously described in detail elsewhere [30].

Participants were followed-up at 2, 5 and 10 years. Clinical examination and ambulatory blood pressure monitoring was only included in the baseline assessment, in 2002, and the 2012 assessment.

Ambulatory Blood Pressure Monitoring

Consenting participants were fitted with a twenty-four hour blood pressure monitor (Spacelabs 90207 – Spacelabs Medical Inc., Redmond, Washington USA). An appropriate sized cuff was fitted to the non-dominant arm. Subjects were instructed to relax their arm when the cuff was inflating. Monitors were programmed to take a BP recording every 30 minutes during the day (7 am to 10 pm) and every hour overnight (10 pm to 7 am). If the monitor failed to obtain a blood pressure recording on the first attempt, it would automatically retry the measurement 2 minutes later.

Three time periods were examined: daytime (10 am – 8 pm), nighttime (midnight – 6 am) and the full 24-hour period [31]. Only studies with at least 16 recordings within 24 hours were included in the analysis. Studies with 10 or more daytime recordings were deemed suitable for daytime analysis and studies with five or more nighttime recordings were deemed suitable for nocturnal analysis [31].

Mean systolic and diastolic blood pressure were calculated for each time period. Blood pressure variability was calculated using the standard deviation (SD) of the mean blood pressures. The coefficient of variation (Cv) of blood pressure (SD / mean BP) was also calculated for each time period.

Clinical Assessment

Past medical history was obtained by direct interview of subjects. Particular attention was paid to presence or absence of cardiovascular disease and risk factors. If participants were unsure of their past medical history, general practice (GP) medical notes were reviewed.

Participants were asked to bring a list of all medications they were taking with them to the assessment. Use of cardioactive medication was defined as using any antihypertensive medication, diuretic, anti-anginal or anti-arrhythmic. Height and weight were recorded and body mass index (BMI) was calculated.

Follow-up Examination

In 2011, surviving participants were invited to take part in a follow-up study if they remained registered with the participating general practice and had not withdrawn from the study at the 2-year or 5-year follow-up assessments. Ten-year follow-up included; clinical assessment and ambulatory blood pressure, measured as described at baseline.

Ethical approval

Ethical approval for the baseline study was provided by the County Durham and Darlington Local Research Ethics Committee. Ethical approval for the follow-up study was granted by the National Research Ethics Service Committee North East- Newcastle and North Tyneside One**.** All participants gave written informed consent.

Analysis

Data were analysed using Statistical Package for Social Science (SPSS) version 19 and R [32] with *lme4* [33] and *lmerTest* [34] packages. For all tests, the level of statistical significance was set at <0.05.

Categorical data are displayed as frequency and percentage. Chi square and Fisher's exact tests were used, as appropriate, to test for differences in the distribution of categorical data.

Normally distributed, continuous data are displayed using mean and standard deviation. Non-parametric data is displayed using median and interquartile range. Normally distributed data

from two unrelated samples were compared using the Student's t-test for independent samples. Repeated measures from two related samples were compared using paired t-tests.

Multilevel modelling with test sessions grouped by participant was used to examine if BP variability was affected by session independent of age, sex, medication and mean BP. The models included a random intercept term by participant.

RESULTS

Study Participants

At baseline, 338 participants underwent ambulatory blood pressure monitoring. At follow-up 104 of these participants consented to participation in the study, 83 of whom underwent successful repeat ambulatory blood pressure monitoring. Figure 1 shows the details of recruitment. Participants lost to follow-up (either due to death or withdrawal from the study) were significantly older than participants who took part in the follow-up examination [Median (IQR) 74 (69-78) v 70 (67-73), P<0.001]. Prevalence of ischemic heart disease, diabetes, hypertension, use of tobacco, and use of antihypertensive medication at baseline did not significantly differ between groups (Table 1). Class of antihypertensive medication prescribed did not differ between groups (Supplementary Table 1). Participants lost to follow-up had significantly greater 24 hour and nighttime mean systolic BP, daytime systolic BP variability and diastolic variability compared to those participating in the follow-up examination (Table 1).

Median numbers of ABPM readings during the 24-hour period at baseline and follow-up was 37 (range 20-40) and 35 (range 18-40) respectively. For the daytime period median number of readings at baseline and follow-up were 19 (range 10-20) and 18 (range 10-20)

respectively and for the nighttime period the median number was 6 (range 5-6) at both baseline and follow-up.

Changes in Ambulatory Blood Pressure Over Time

Data from the 83 participants with BP recordings at baseline and follow-up were analysed. Mean BP did not

Mean BP did not significantly differ between baseline and follow-up for any of the time periods examined (

periods examined (

Table 2). Twenty-four hour and daytime systolic and diastolic BP standard deviation (SD) were significantly greater at follow-up than at baseline (Table 3). Similarly, 24 hour and daytime systolic and diastolic co-efficient of variation (Cv) were significantly greater at follow-up compared to baseline (Table 3). None of the nighttime measures of variability significantly differed between baseline and follow-up.

Changes in Comorbidities and Use of Medication over Follow-up

Comorbidities and medication use at baseline and follow-up were compared for the 83 individuals who underwent ABPM at both examinations. There was a significant increase in the number of individuals reporting a past medical history of hypertension at follow-up compared to baseline [60% v 37% respectively, P=0.005]. Similarly, the number of individuals diagnosed as diabetic had increased [2% v. 15%, P=0.001].

The percentage of patients taking antihypertensive medication increased from 46% at baseline to 69% at follow-up (P=0.003). Examining use of individual antihypertensive medication classes showed that there was a significant increase in the number of participants prescribed calcium channel blockers [14% v 30% (P=0.015)], angiotensin 2 receptor blockers [4% v 17% (P=0.005)] and diuretics [17% v 36% (P=0.005)]. Use of angiotensin converting

enzyme inhibitors [29% v 13% (P=0.013)] and beta-blockers [24% v 17% (P=0.183)] had decreased.

To examine if increased use of cardioactive medication may account for the increase in ABPV, a subgroup of 19 patients not taking cardioactive medication at baseline or at follow-up was examined. These patients had no history of cardiovascular disease or diabetes. Twenty-four hour and daytime systolic and diastolic blood pressure SD were significantly greater at follow-up than at baseline in this subgroup (Table 3). Similarly, the coefficient of variation significantly increased between baseline and follow-up (Table 3). Twenty-four hour, daytime and night-time mean systolic blood pressure were also significantly greater at follow-up than at baseline in this subgroup (

Table 2)

Predictors of ABPM Variables

Finally multilevel modelling was used to examine if association between session and BP variability was independent of potential confounders. The initial model included; age at baseline, sex, use of antihypertensive medication, mean blood pressure and follow-up interval represented by months between ABPM recordings. An interaction term sex*months between recordings was also added to the model to examine if the effect differed for men and women. Results are shown in (Table 4). Follow-up interval had a significant, positive effect on the 24-hour and daytime blood pressure variability, measured by BP standard deviation, independent of participant age, sex and use of antihypertensive medication. The interaction between sex and follow-up interval was of borderline significance in models of 24 hour and daytime systolic SD (P= 0.078 and P=0.055 respectively). Suggesting a trend towards greater blood pressure variability in women.

The analysis was repeated with co-efficient of variation (Cv) as the dependent variable and age at baseline, sex, use of antihypertensive medication, follow-up interval and sex*follow-

up interval an interaction term. Follow-up interval was a significant and positive predictor of 24 hour and daytime but not nighttime Cv.

The models were rerun adding body mass index, history of diabetes, alcohol consumption and smoking history (in pack/years) to the model as predictors. None of these variables were significant predictors of BP variability and did not alter the fit of the model (data not shown). Analysis was also repeated substituting number of antihypertensive medications for use of antihypertensive medication. This did not significantly alter the model or significant predictors.

Finally analysis was run with use of individual antihypertensive medication (ace inhibitor, ARB, Alpha-blocker, Beta antagonist, diuretic and calcium channel blocker) replacing use of any hypertensive medication. Follow-up interval remained a significant predictor of BP variability measure as either SD or Cv. Individual medication classes did not have a significant effect on BP variability (Supplementary data).

DISCUSSION

In this study, we have shown that 24 hour and daytime ambulatory blood pressure variability (measured as standard deviation or co-efficient of variation) increased among community dwelling older people over a ten-year follow-up interval whereas mean blood pressure did not significantly change. Over recent decades, great strides have been made in controlling mean BP. It is therefore interesting to find, that even when mean BP is stable, BP variability increases. BP variability has been identified as a risk factor for cardiovascular disease and mortality independent of the mean BP [9-17]. To date, very little attention has been paid to

monitoring or controlling ABPV and it remains unknown what degree of BP variability is harmful.

It has been suggested that ABPV may be an additional target for treatment over and above mean BP [35]. Animal model show that control of BP variability is associated with reduced end organ disease [36]. In this study use of antihypertensive medication was not associated with BP variability. Nor were specific antihypertensive classes associated with BP variability. Previous studies have shown that calcium channel blockers and diuretics have greater effect on BP variability compared to other antihypertensive [27-29]. Failure to reproduce this finding here may reflect type 2 error resulting from the relatively small number of participants taking each class of medication.

Our observation that BP variability increases over a ten year follow-up is in contrast to the findings of Goldstein et al. who reported that ambulatory blood pressure variability among older people decreased over a five-year follow-up [26]. Goldstein et al.'s cohort was highly selected and was unrepresentative of the general older population. Participants with a history of hypertension, obesity, impaired cognitive abnormalities or psychiatric disorders were excluded from the Goldstein study. In contrast, the population examined here was more typical of the general older population. It must still, however, be acknowledged that there was high attrition in this study. The individuals participating in the follow-up study were, in general, younger, with lower mean BP and lower BP variability than participants lost to follow-up, suggesting follow-up participant may represent a selected cohort at lower cardiovascular risk.

Although our findings are not in keeping with Goldstein et al findings, they are in keeping with cross-sectional studies showing a relationship between age and ABPV [10,18,19]. Sakakura et al. compared blood pressure variability among a group of 101 younger elderly (aged 61-79) and 101 older elderly (aged ≥80). Blood pressure variability was significantly greater among the older group compared to the "young elderly" [10]. Cincconetti et al. found that BP variability is greater among older hypertensive patients compared to younger hypertensive patients and that age and BP variability were significantly correlated in men and women [19].

It is not surprising that BP variability increases with age. Increased ABPV is associated with decreased baroreceptor sensitivity and arterial compliance [20-23]. Both baroreceptor sensitivity and arterial compliance decrease with age [24 25]. Interestingly nocturnal BP variability did not significantly change. This may reflect type II error. Only 65 individuals met the criteria for inclusion in the nocturnal analysis (≥5 ABP readings) compared to the 76 who met the criteria for daytime analysis. Alternatively the greater increase in daytime BP variability compared to nighttime variability may reflect BP lability in response to physical and mental exertion during waking hours. At both time points BP variability was greater during the daytime than at nighttime. Conditions associated with exaggerated changes in BP in response to day-to-day activities e.g. orthostatic hypotension and postprandial hypotension all become more common in later life [30,37,38]. Age has also been associated with greater BP variability in response to mental stress [39]. It is possible, that these fluctuation in BP in response to normal activities of daily living have greater influence on daytime ABPV than nocturnal ABPV.

Although ABPV increased over ten year. Mean BP did not significantly change over the follow-up period. The stability of mean systolic or diastolic BP over the ten-year follow-up period is interesting. Most studies using casual or ambulatory BP monitoring show an

increase in blood pressure with increasing age. The absence of an increase in mean BP in this cohort may reflect changes in the management of hypertension over the last ten years, including; better detection of hypertension, increasing use of antihypertensive medication and tighter blood pressure control among older hypertensive patients. At baseline, the most up-to-date UK hypertension guidelines recommended antihypertensive drug therapy for all individuals with sustained BP >160/100 and treatment of individual with BP >140/90 according to target organ damage and ten-year coronary heart disease risk [40]. Low dose thiazide diuretics and beta-blockers were the preferred first-line antihypertensives. Over the intervening ten years, between the baseline and follow-up assessment, there have been significant changes to the UK guidelines on the management of hypertension. The 2011 NICE hypertension guidelines advocated widespread use of ABPM to confirm hypertension in all individuals with office blood pressure >140/90 [2]. Calcium channel blockers and thiazide-like diuretics are now recommended as first-line management for people aged over 55. In addition, the guidelines recommend that individuals aged over 80 years are offered the same antihypertensive drug treatment as people aged 55-80 [2]. These changes are reflected in the changes to prescribing patterns observed in this study. This move towards more accurate diagnosis of hypertension and tighter control of blood pressure in all age groups may account for failure of this study to reproduce the increase in mean blood pressure observed in other studies. Mean BP did increase among the 19 individuals not taking cardioactive medication, supporting the suggestion, that the lack of a significant increase in mean BP among the wider study population may be due to the increased use of effective antihypertensive medication.

A number of limitations should be acknowledged. This was a post hoc analysis from a large study designed to look at a number of aspects of neurocardiovascular function in older people. Attrition over the ten-year follow-up was high. This resulted in a relatively small

follow-up sample that was younger and fitter at baseline compared to the original cohort. The small follow-up population may have resulted in type 2 error particularly when examining the influence of medication class on BP variability where the numbers in each group were small. Conversely the selection bias of younger fitter individuals may have led to an underestimation of changes in ABPV as ABPV would be expected to increase more in participants with greater burden of cardiovascular disease.

One of the challenges of comparing ambulatory blood pressure studies is the variety of methodologies used to collect BP data. In this study, we used fixed periods for daytime and nighttime. This method meant data from morning and late evening periods were not included in the analysis of daytime and nighttime data. It could be argued that such methods risk excluding important contributions to BP variability such as the morning surge. However, using narrow fixed time periods avoids errors due to inaccuracies in patients' diaries and differences in patients wake sleep patterns associated with age. The use of fixed day/night windows is now recommended [41].

Debate has long existed on the number of recordings required for satisfactory ABPM recordings. Since the inception of this study in 2002, international efforts have been made to standardise ABPM protocols. In 2013, the European Society of Cardiology released a position paper suggesting blood pressure readings should be made at 30 minute intervals and that recordings required at least 20 valid daytime readings (0900-2100) and 7 valid night-time readings (0100-0600) [41]. Although the shorter daytime window used in this study and the decision to record BP hourly overnight meant our protocol did not quite reach current ESC criteria, the majority of participants had 18 or more daytime recordings and 6 or more nocturnal recordings at both assessments. Suggesting that although the studies original

criteria only demanded a 50% successful inflation rate the vast majority of patients had well above the 70% successful inflation rate suggested by the recently published ESC guidelines [41].

It should also be noted that if hypertension was diagnosed on baseline ambulatory BP monitoring it was essential for ethical reasons that the participants general practitioner was informed and blood pressure monitored and treated as appropriate. It is therefore possible that changes in mean BP and BP variability are not representative of those seen in an unmonitored population. However, since 2004, general practitioners in the UK have been financially incentivised to identify and effectively manage hypertension in their patients. It is, therefore, likely that the monitoring of BP that participants received as a result of participating in this study is not too different from that offered to the general population.

The underlying mechanisms causing ABPV to increase over time were not examined in this study. Future work will examine the contribution of baroreceptor sensitivity, arterial stiffening and response to physical and mental stress.

These limitations aside, this study is the first to observe that ABPV increased over a ten-year follow-up. This was despite stable mean BP and independent of medication. These findings are important as increased ABPV is associated with adverse cardiovascular outcomes and has recently been suggested as an additional target for treatments aimed at reducing cardiovascular risk [35]. If ABPV is to become a target for treatment, further studies are needed to determine how different antihypertensive classes effect ABPV and what degree of ABPV should be considered harmful.

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